Polyglandular endocrinopathy type II (Schmidt's syndrome) in a Dobermann pinscher

POLYGLANDULAR ENDOCRINOPATHY TYPE II (SCHMIDT'S SYNDROME) IN A DOBERMAN PINSCHER

Abstract

A 3-year-old, female neutered, Doberman pinscher was presented for investigation of lethargy, episodic collapse, ataxia and myxoedema. Primary hypothyroidism and primary cortisol deficient hypoadrenocorticism were diagnosed based on history, physical examination and compatible hormonal analysis. Increased serum concentrations of thyroglobulin autoantibodies and 21-hydroxylase autoantibodies indicated an immune-mediated aetiology. The case was complicated by lymphadenopathy with hand-mirror lymphocytes, classically identified in lymphoma. A PCR test for antigen receptor rearrangement (PPAR test) indicated polyclonality and therefore reactive lymphadenopathy. The dog's clinical signs resolved following introduction of levothyroxine and prednisolone. Prioritising the problem-based approach in this case facilitated the diagnosis of hypoadrenocorticism in addition to hypothyroidism due to the persistence of clinical signs despite thyroxine replacement. Importantly, atypical adrenal gland dysfunction was not misinterpreted as inadequate therapeutic response to thyroxine supplementation. The observation that polyglandular endocrinopathy type II can occur in dogs suggests that in dogs with a suboptimal response to treatment for hypothyroidism or hypoadrenocorticism comorbid endocrinopathies should be investigated.

Introduction

Comorbid endocrinopathies are rare in dogs and polyglandular autoimmune endocrinopathies are even less common. The most frequently reported comorbid endocrinopathies are hyperadrenocorticism and diabetes mellitus, however this combination is not autoimmune (Peterson *et al* 1981). A recent case series reported 2.3% of dogs admitted to a referral clinic with endocrine disease had comorbid endocrinopathies (Blois *et al* 2011). Of these, 7 (20%) were diagnosed with hypothyroidism and hypoadrenocorticism (4 of which had glucocorticoid deficient hypoadrenocorticism, though aldosterone concentrations were not reported), however this study did not report whether these cases were autoimmune. Other than this series, comorbid hypothyroidism and glucocorticoid deficient hypoadrenocorticism has been reported as an isolated case report in a Boxer (Kooistra *et al* 1995). Another dog is reported with typical hypoadrenocorticism (mineralocorticoid and glucocorticoid deficiencies) in addition to hypothyroidism (Pikula *et al* 2007). To date none of the reports of comorbid hypothyroidism and glucocorticoid deficient hypoadrenocorticism have demonstrated immune mediated adrenalitis. This report describes a dog with comorbid endocrine disease, similar to Schmidt's syndrome, the type-II polyglandular syndrome

described in humans. The report presents serological evidence for immune-mediated adrenalitis, comparable to the situation often identified human cases. Schmidt's syndrome is the most common (poly)immunoendocrinopathy in humans, characterised by both autoimmune adrenalitis and thyroiditis and/or type I diabetes mellitus (Gupta and Nagri 2012).

Case history

A 3-year-old female neutered Doberman pinscher was referred due to progressive weight gain, poor coat condition and lethargy for 6 weeks. Over the past week she had developed polydipsia, generalised weakness and episodic collapse. On examination she was depressed and had a high body condition score 7/9. She was hypothermic (rectal temperature 35.9°C) with tacky oral mucous membranes and a relative bradycardia (44bpm) with poor peripheral pulse quality. She had myxoedema of the head, a brittle hair coat, pinna margin crusting and thickened skin. She had submandibular, prescapular and popliteal lymphadenopathy. Thoracic and cardiac auscultations and abdominal palpation were unremarkable. Neurological examination revealed mild ataxia and reduced conscious proprioception with retained spinal reflexes.

Following admission, the dog was actively warmed and provided with intravenous fluid support. Serum biochemistry and complete blood count were performed (Table 1). These revealed an equivocal increase in alanine aminotransferase and creatinine kinase, a mild azotaemia, a mild increase in cholesterol and triglyceride concentrations along with non-regenerative anaemia. Electro and echocardiograms were both unremarkable. A strong clinical suspicion for hypothyroidism meant total thyroxine and thyroid stimulating hormone (TSH) concentrations were measured. Reduced total thyroxine and increased TSH concentrations indicated primary hypothyroidism (Nelson 1991). An increase in thyroglobulin autoantibody concentrations confirmed immune-mediated thyroiditis (Table 2). The myxoedema and demeanour improved within 48 hours of initiating levothyroxine[a]. Despite the improvement, the generalised weakness and lymphadenopathy persisted. Given the absence of a stress leucogram and persistent weakness, resting cortisol concentration was measured and the result did not exclude hypoadrenocorticism (Table 2). Adrenal function testing was therefore performed using an adrenocorticotrophic hormone (ACTH) stimulation test, which confirmed hypoadrenocorticism (Table 2). A normal aldosterone response at 60 minutes post-ACTH stimulation, normal serum electrolytes, normal renin concentration and increased ACTH concentration, suggested primary cortisol deficient hypoadrenocorticism (Feldman 2004 and Thompson *et al* 2007). An increased serum concentration of 21-hydroxylase autoantibodies (21-OHAb) suggested immune-

mediated adrenalitis (Rick *et al* 2013). Glucocorticoid replacement (prednisolone 0.25mg/kg PO SID) normalised the dog's demeanour and the weakness resolved within 24 hours; there were no further episodes of collapse.

Due to persistent peripheral lymphadenopathy, fine needle aspirates were obtained. These revealed small homogenous hand-mirror lymphocytes suspicious for lymphoma (Zaharopoulos *et al* 1990). Thoracic radiographs and abdominal ultrasound were unremarkable; aspirates of the liver and spleen revealed no evidence for mirror-handle lymphocytes. A polymerase chain reaction test for antigen receptor rearrangement (PARR test) was performed on the lymph node aspirates (Pate *et al* 2011). This revealed polyclonality, consistent with lymph node hyperplasia not neoplasia.

A final diagnosis of autoimmune polyglandular disease was made, akin to Schmidt's syndrome in people (Gupta and Nagri 2012 and Neufeld *et al* 1990), with concomitant lymph node hyperplasia.

The clinical signs and the lymphadenopathy resolved within a week of discharge. After 4 weeks, the dog's body condition score had improved. The dog was brighter, the dermatological changes had improved and the reminder of the clinical examination was unremarkable. Biochemistry revealed a mild improvement in the cholesterol (Table 3), a mild increase in ALT and ALP were likely due to metabolic hepatopathy. At the time of writing, 3 years post-diagnosis, the dog remains well and continues to receive thyroid and glucocorticoid replacement. No electrolyte abnormalities have developed to suggest development of overt mineralocorticoid deficiency or hyperglycaemia to suggest diabetes mellitus.

Discussion

Polyglandular endocrinopathies are uncommon in people and dogs (Betterle *et al* 2004 and Blois *et al* 2011). A canine case series by Blois *et al* (2011), suggested hypothyroidism and hypoadrenocorticism was the second most common combination after hyperadrenocorticism and diabetes mellitus. As seen in this case, glucocorticoid deficient hypoadrenocorticism can be challenging to diagnose due to the absence of pathognomonic signs and insidious disease progression; there is still controversy regarding appropriate screening in humans (Cutolo 2014). Baumstark et al (JVIM 2014) demonstrated that the majority of dogs diagnosed with primary hypoadrenocorticism with unremarkable electrolyte concentrations do have aldosterone deficiency. In this case, aldosterone concentration did rise following ACTH administration and plasma renin was not elevated indicating true isolated cortisol-deficient hypoadrenocorticism. In this case, as with previous reports, hypothyroidism was diagnosed first followed by hypoadrenocorticism (Kooistra *et al* 2008 and Pikula *et al* 2007). However, compared to previous reports, this dog had both endocrinopathies identified within 72 hours. By contrast, the

first endocrinopathy identified in humans is typically hypoadrenocorticism (Gupta and Nagri 2012). It has been reported that initiating thyroxine replacement in Schmidt's syndrome prior to glucocorticoid replacement can precipitate an adrenal crisis due to enhanced hepatic corticosteroid metabolism and a general increase in metabolic rate (Betterle *et al* 2004). Despite the introduction of levothyroxine in this case prior to glucocorticoid replacement, an adrenal crisis was not observed, possibly due to the short interval between introducing supplementation. It is possible that this dog would have been discharged and suffered an acute adrenal crisis pending a review of her thyroid disease without further investigations if additional differentials for her persistent lethargy and collapse had not been considered. In people, subclinical polyglandular disease is often overlooked, as polyglandular function testing is rarely performed at the time of initial presentation (Betterle *et al* 2004).

Schmidt's syndrome in humans is an autoimmune condition (Betterle *et al* 2004). In this dog measurement of 21-OHAb and anti-thyroglobulin antibody concentrations confirmed a similar aetiology. 21-OHAb have been identified in 30% of dogs with hypoadrenocorticism, with a specificity of 95% (Rick *et al* 2013). In this case, the increase in 21-OHAb in conjunction with compatible clinical findings and biochemical results provided strong evidence for autoimmune adrenalitis. This is consistent with their use in humans (Betterle *et al* 2005). As with anti-thyroglobulin autoantibodies in dogs, a cohort of humans have circulating 21-OHAb in the absence of adrenal insufficiency (Betterle *et al* 2005). The frequency with which 21-OHAb occur in a larger cohort of normal dogs remains to be determined (Kooistra *et al* 1995, Pikula *et al* 2007, Rick *et al* 2013). In addition to direct immune mediated destruction of the thyroid and adrenal glands in canine Schmidt's syndrome, lymphocytic adenohypophysitis has also been reported (Adissu *et al* 2010). This seemed unlikely in this case due to elevated concentrations of both ACTH and TSH. Diabetes mellitus (DM) is present in a subset of humans with Schmidt's syndrome, however was not encountered in this dog at any point (Gupta and Nagri 2012 and Betterle *et al* 2004). Interestingly, humans may also have antibodies to pancreatic antigens but never develop overt DM; these have not been measured in this dog at the time of writing.

The dog's azotaemia was suspected to result from a combination of hypovolaemia and reduced GFR due to the hypothyroidism (Panciera and Lefebvre 2009). Intravenous fluid therapy and thyroxine replacement are likely to have both contributed to normalisation prior to discharge and sustained resolution of the azotaemia. Unfortunately this cannot be verified in the absence of a urinalysis at the time of arrival

Hand-mirror lymphocytes result from intracellular incorporation of immune-complexes (McGraw *et* al 1981, Zaharopouls *et al* 1990). Most references to hand-mirror lymphocytes relate to lymphoproliferative disease (Schumacher *et al* 1978 and Thomas *et al* 1980), however these are also

seen during cell migration and immune stimulation (Biberfeld *et al* 1970 and Hyun *et al* 2012). There are however no reports of lymphadenopathy with hand-mirror lymphocytes in association with endocrinopathies. In this dog we suspect they were secondary to immune-mediated disease (as demonstrated by the elevated TGAA and 21-OHb). Future investigations into the lymphoid populations in dogs with comorbid endocrinopathies would clarify this point.

This case emphasises the importance of a systematic clinical approach based on problems and differentials and cautions against pattern recognition as a sole means of directing diagnostic testing. Should this approach not have been followed in this case, the hypoadrenocorticism would have been missed and the dog's condition could have worsened due to the introduction of thyroxine and precipitation of an adrenal crisis. It emphasises the value of screening for concurrent endocrinopathies in dogs where clinical abnormalities persist. This is particularly significant due to the increasing frequency with which glucocorticoid deficient hypoadrenocorticism is being recognised in dogs presenting with normal electrolyte concentrations (Behrend and Kennis 2010 and Baumstark *et al* 2014).

Footnote

[1] 0.02mg/kg PO q12hrs, Thyforon, Dechra (manufacturer has subsequently replaced with Forthyron)

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Table 1: Biochemistry and Haematology

Biochemistry		
Test	**Result**	**Reference range**
Total protein	73 g/L	(54.0 -77.0)
Albumin	32 g/L	(26.0 -40.0)
Globulin	41 g/L	(20.0 -47.0)
Sodium	143 mmol/L	(139 -154)
Potassium	5.2 mmol/L	(3.5 -6.0)
Na:K ratio	28	(25.0 -35.0)
Chloride	107 mmol/L	(99 -125)
Total calcium	2.58 mmol/L	(2.0 -3.0)
Phosphate	1.40 mmol/L	(0.8 -1.6)
Urea	* 9.8 mmol/L	(2.0 -9.0)
Creatinine	* 156 umol/L	(40.0 -106.0)
ALP	12 U/L	(0.0 -25.0)
ALT	* 77 U/L	(0.0 -25.0)
GLDH	5 U/L	(0.0 -10.0)
Total bilirubin	1 umol/L	(0 - 9.0)
Bile acids	1 umol/L	(0 - 10.0)
Glucose	3.49 mmol/L	(3 - 7)
CK	* 376 U/L	(0.0 -190.0)
Cholesterol	* 8.6 mmol/L	(3.8 -7.0)
Triglycerides	* 3.8 mmol/L	(0.45 -1.9)
Amylase	1616 U/L	(0.0 -1800.0)
Lipase	49 U/L	(0.0 - 150.0)
Haematology		
RBC	* 4.05 x10^12/L	(5.0 -8.5)
Hb	* 10.0 g/dl	(12.0 -18.0)
HCT	* 29.5 %	(37.0 -55.0)
MCV	72.8 fl	(60.0 -80.0)
MCH	24.7 pg	(19.0 -26.0)
MCHC	33.9 g/dl	(31.5 -37.0)
Platelets	311 x10^9/L	(160 -500)
WBC	7.10 x10^9/L	(6.0 -15.0)
Neutrophils	5.68 x10^9/L	(3.0 -11.5)
Bands	0.14 x10^9/L	(0.0 -0.3)
Lymphocytes	* 0.99 x10^9/L	(1.0 -4.8)
Monocytes	0.14 x10^9/L	(0.0 -1.3)
Eosinophils	0.14 x10^9/L	(0.0 -1.25)

Table 2: Endocrine testing

Test	**Result**	**Reference Range**
Thyroxine (Microgenics)	7.5 Low nmol/L	13.0 - 51.0

Free T4 (equilibrium dialysis RIA)	* <2.0 pmol/l	7 - 40
Canine Serum TSH	1.06 High ng/mL	0.00 - 0.50
Thyroid antiglobulin antibody	* 716 %	<200
Adrenal Axis Testing		
Cortisol Basal (RIA)	* <20 nmol/l	28 - 250
Cortisol post ACTH (RIA)	* <20 nmol/l	200 - 400
21-Hydroxylase (optical density measurement) 0.224 (hypoadrenocorticism >0.2)		
Aldosterone	126 pmol/l	0 - 960
Aldosterone post ACTH (RIA)	326 pmol/l	200 - 2100
Endogenous ACTH Assay	* 104 pg/ml	20 - 80
Plasma Renin	1.85 ng/mL/hr	0.22 - 2.4

RIA: Radioimmunoassay

Table 3: Biochemistry (4 weeks post start of therapy)

Biochemistry (4weeks after thyroid supplementation and prednisolone)		
Test	**Result**	**Reference range**
Total protein	76 g/L	(54.0 -77.0)
Albumin	39 g/L	(26.0 -40.0)
Globulin	37 g/L	(20.0 -47.0)
Sodium	144 mmol/L	(139 -154)
Potassium	4.6 mmol/L	(3.5 -6.0)
Na:K ratio	31	(25.0 -35.0)
Chloride	104 mmol/L	(99 -125)
Total calcium	2.80 mmol/L	(2.0 -3.0)
Phosphate	* 2.00 mmol/L	(0.8 -1.6)
Urea	8.9 mmol/L	(2.0 -9.0)
Creatinine	94 umol/L	(40.0 -106.0)
ALP	*66 U/L	(0.0 -25.0)
ALT	* 35 U/L	(0.0 -25.0)
GLDH	4 U/L	(0.0 -10.0)
Total bilirubin	2 umol/L	(0 - 9.0)
Bile acids	3 umol/L	(0 - 10.0)
CK	132 U/L	(0.0 -190.0)
Cholesterol	* 7.3 mmol/L	(3.8 -7.0)
Triglycerides	* 3.8 mmol/L	(0.45 -1.9)
Amylase	1616 U/L	(0.0 -1800.0)
Lipase	49 U/L	(0.0 - 150.0)